ABRA

The International Authority for the Source Plasma Collection Industry

P.O. Box 669 • Annapolis, MD • USA • 21404-0669
Tel: 410.263.8296 • Fax: 410.263.2298
www.plasmainfo.org

October 18, 1999
Reference Number: FDAA99001

Dockets Management Branch (FDA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

RE: Comments on FDA's Guidance for Industry – Revised Precautionary Measures to Reduce Possible Risk of Transmission of Creutzfeldt-Jakob Disease and New Variant Creutzfeldt-Jakob Disease by Blood and Blood Products

ABRA is pleased to provide these comments on the Food and Drug Administration's (FDA) recently promulgated revised guidance addressing precautionary measures to reduce the risk of transmission of Creutzfeldt-Jakob Disease (CJD) in blood and blood products (hereinafter, the CJD Guidance). ABRA is the trade association and standards setting organization for the Source Plasma collection industry. ABRA represents the interests of approximately 400 plasma collection centers nation-wide. These centers are responsible for the collection of nearly 11 million liters of Source Plasma annually. This plasma makes-up roughly 60% of the world's plasma supply and is manufactured into life supporting and life sustaining medicines.

As Agency officials have acknowledged, the nation's supply of blood and blood products is safer than it has ever been. Nonetheless, industry, FDA and the consuming public must be ever vigilant for potential threats to the blood supply. As such, ABRA applauds the Agency's vigilance regarding blood and blood products with respect to Creutzfeldt-Jakob Disease (CJD) and new variant Creutzfeldt-Jakob Disease (nvCJD).

I. Introduction

While it is appropriate for FDA to develop policies aimed at potential and even theoretical threats to the blood supply, in such cases strict adherence to administrative procedures, such as public notice and comment, is of paramount importance. This is because potential and theoretical threats, by definition, do

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not present an imminent threat to the safety of the blood supply. Thus, the balance between perceived gains in product safety from theoretical threats to the blood supply and the impact of such policies on the regulated industry and the continued availability of blood and blood products, must be carefully struck. Nowhere is the need for this careful balance more evident than the recent CJD Guidance.

ABRA and its members believe that given the current state of scientific evidence regarding the transmissibility of nvCJD, it is premature to require the deferral of donors that have spent a cumulative six months or more in the United Kingdom between 1980 and 1996. The lookback and product retrieval requirements associated with deferral of U.K. donors are even more troubling given the lack of adherence to administrative procedures in the development of these aspects of the new policy. Similarly, the change in Agency policy regarding deferral of donors at risk for classical CJD due to familial risk factors without the appropriate public process should not be permitted to stand. Finally, the Agency's reliance on the phrase "readily retrievable records" in this and other FDA Guidance is inappropriate given the lack of clear definition for what constitutes "readily retrievable records."

In light of the theoretical nature of the perceived nvCJD risk, there exists no imminent public health concern that would justify immediate implementation of the CJD Guide. In addition, due to the lack of adherence to administrative procedures and public process including the utilization of advisory committees, the lookback requirements and the deferral of donors at risk for classic CJD due to familial risk factors, we request that implementation of the Guide be suspended until such time as these changes can be fully considered by the appropriate Advisory Committees and an adequate opportunity has been provided for public comment. Furthermore, we request that the Agency use the CJD Guide as an opportunity to define "readily retrievable records" as those records that are either located at the blood establishment in hard copy or those that are computer archived.

II. Immediate Implementation of the CJD Guide

The CJD Guide is intended to address a theoretical risk, not an imminent threat to the safety of blood and blood products. Although the CJD Guide states that there are "public health reasons for immediate implementation" of the Guide, no such reasons are described in the Guide. In fact, the CJD Guide states that the "transmission of the CJD infectious agent by blood products is highly unlikely." (CJD Guide at §II.A). This acknowledgement belies the assertion that public

health concerns necessitate immediate implementation of the CJD Guide. Consequently, we request that the Agency withdraw the CJD Guide and reissue it as a draft Guide for public comment and consideration.

The absence of an imminent public health concern is further supported by the fact that the TSE Advisory Committee struggled with the decision to defer U.K. donors and acknowledged that its recommendations were not based on complete scientific evidence. In fact, the final Committee vote was close and at one point, the Committee considered excluding plasma products from the requirement altogether. Moreover, at no time did the Committee consider or discuss a lookback requirement in conjunction with the deferral of U.K. donors. Given the lack of clear mandate from the Committee regarding U.K. donor deferral and the theoretical nature of the putative risk, there exists no public health basis upon which immediate implementation of the CJD Guide could be justified.

The need for dissemination of a draft CJD Guide is made more important by the fact that significant changes to previous Agency policy were included in the recent CJD Guide without input from Agency stakeholders. As discussed more fully below, the lookback requirements for prior donations from U.K. donors and the change in definition of familial risk factors for classic CJD, represent significant and burdensome policy changes that were not vetted through the public process. Thus, at a minimum, the Agency should provide the regulated industry and consuming public the opportunity to meaningfully comment on these policies through dissemination of a draft CJD Guide without an expectation of imminent compliance with the Guide.

III. Utilization of FDA Advisory Committees

The U.K. donor deferral policy was developed almost exclusively through consultation and advise from the TSE Advisory Committee. While the use of advisory committees is an important part of the FDA policy development process, it is essential to the development of sound policy that advisory committees are consulted only on issues within the collective expertise of their membership. This was not the case for the development of the U.K. donor deferral policy.

The TSE Advisory Committee is made up of renown experts in the field of spongiform encephalopathies and neurology. However, the collective expertise of the committee is notably lacking with respect to hematology and blood products. Thus, while it was appropriate for the TSE Advisory Committee to advise the Agency with respect to the risk of transmission of nvCJD from individuals who traveled to the U.K., it was not within the purview of this

Committee to consider a U.K. donor deferral policy. Issues of blood policy such as this fall squarely within the mandate of the Blood Products Advisory Committee (BPAC).

In order to obtain the appropriate advice and counsel on a policy as broad-sweeping as U.K. donor deferral, the Agency should have consulted the TSE Advisory Committee only with respect to the risk of nvCJD transmission and should consult the BPAC with respect to the impact of such a policy on blood and blood products. Although a few standing BPAC members sat as temporary members of the TSE Advisory Committee during the relevant deliberations, the participation of these individuals alone, was not sufficient to adequately inform the decision-making process. It is also noteworthy that each of the BPAC members who sat on the TSE Advisory Committee voted against the U.K. donor deferral policy.

Consideration of the U.K. donor deferral policy also should be taken to the Department of Health and Human Services Advisory Committee on Blood Safety and Availability (ACBSA). The ACBSA is uniquely charged with the responsibility of balancing the scientific risks and benefits with the societal and economic impacts of proposed blood policies. With this mandate, and with appropriate input from BPAC and the TSE Advisory Committee, the ACBSA can more completely consider the many and far reaching implications of a U.K. donor deferral policy.

Without input from the appropriate advisory committees, and the public debate that would flow from it, the process by which the U.K. donor deferral policy was developed was seriously flawed. As a result, we request that the CJD Guide be withdrawn until such time as it is given adequate and complete consideration by all appropriate advisory committees including the BPAC and the ACBSA. Sound blood policy only can be assured through appropriate utilization of all relevant advisory committee expertise.

IV. Lookback Requirements for U.K. Donors

Although the Transmissible Spongiform Encephalopathy (TSE) Advisory Committee considered the issue of U.K. donor deferral at length, the FDA sought no advise regarding other regulatory consequences that may flow from this decision. More specifically, no advisory committee was asked to consider whether previous donations from such donors should be identified and, to the extent possible, retrieved. In short, FDA asked the Committee whether such

donors should be deferred but did not ask whether lookbacks should be performed. Thus, the Committee was not given an opportunity to engage in the kind of risk-benefit analysis that otherwise informs agency policy setting.

Moreover, because this issue was not brought before the any advisory committee, the regulated industry and consuming public were not given notice that the Agency was considering such an approach. In fact, on numerous occasions Agency officials informally stated no lookback requirement was being considered and that the CJD Guide only would require U.K. donor deferral. Failure to bring this issue to the Committee is tantamount to failing to provide public notice of the Agency's intent to adopt such a policy. Furthermore, because the CJD Guide including this policy was promulgated as a final Agency guidance, and not as a draft, the Agency has not met its statutorily mandated obligation to provide an opportunity for meaningful public comment. Consequently, we request that this requirement be suspended until such time as it can be fully considered by the appropriate advisory committees and the regulated industry has had an opportunity to asses its impact.

The lookback requirement for prior donations of U.K. donors would be unduly burdensome to industry. As currently written, the CJD Guide would require lookbacks to 1980 for all prior donations from donors that had spent an aggregate six months or longer in the U.K. between 1980 and 1996. All implicated prior donations, once identified, would have to be traced to the point of ultimate disposition to verify that they had been pooled for manufacture into plasma derivatives. The administrative burden associated with this activity is staggering. Given the fact that performing the lookbacks will merely serve to confirm that vast majority of the implicated donations already have been pooled, imposition of a lookback requirement for prior donations from U.K. donors is unwarranted and unnecessary insofar as it does not add any increased assurance of safety.

V. Familial Risk Factors for Classic CJD

Previous Agency guidance on donor at increased risk for CJD stated "plasma derivatives prepared from donors with a history of ***multiple blood relatives*** with CJD . . . should be quarantined and destroyed appropriately." (December 11, 1996 CBER memorandum regarding CJD, emphasis added.) In addition, the previous guidance stated:

> . . . A single case of CJD in a family is most likely sporadic rather than due to a genetic mutation. Thus it is unlikely that relatives of a single case of CJD would be at increased risk for developing CJD. Therefore, if the donor's response to questioning indicates a family history of CJD, the donor should be further questioned about the number of family members either diagnosed with CJD or determined to be at risk for developing CJD. . . . (Id.)

Based on these statements and others, industry generally interpreted the previous Agency policy regarding familial risk factors for CJD as being limited to circumstances where more than one blood relative had been diagnosed with CJD.

In contrast, the new CJD Guide requires donor deferral if only one blood relative has been diagnosed with CJD. Although the new CJD Guide does include a reentry algorithm for donors with one blood relative diagnosis of CJD, this change in policy was effected without notice to the regulated industry. Like the lookback requirement, implementation of this change in policy regarding familial risk for CJD should be suspended until the appropriate advisory committees have been given an opportunity to consider it and the public has been given and opportunity to comment.

VI. Definition of Readily Retrievable Records

FDA has used the phrase "readily retrievable records" in connection with the lookback requirement outlined in the CJD Guide and other Agency guidance (e.g., the HCV Lookback Guidance). However, nowhere is the phrase defined. This lack of definition has caused substantial confusion within the regulated industry. Before implementing policies that rely on this phrase, the Agency should provide a clear and rationale definition of what constitutes "readily retrievable records."

Due to the lengthy recordkeeping requirements associated with Source Plasma, records in excess of 10 years are likely to exist. However, the existence of such records does not mean they are readily retrievable. In fact, older records often are stored off-site in warehouse facilities that provide document retention services. More importantly, the due to the evolution of good manufacturing practices (GMPs), older records are less likely to be maintained in accordance with the manner that such records would be maintained today. Consequently,

even when such records do exist, they may not exist in a format that makes them amenable to retrieval and analysis.

The advent of computers, however, has provided new opportunities for more complete and accurate record retrieval. Furthermore, computerized records typically are much more readily retrievable than archived hard-copy records. For these reasons, we believe that the Agency should define the phrase "readily retrievable records" to mean those records that are on-site or other records that are retrievable in an electronic format through a validated document management system. This definition will help ensure the integrity of the archived records that are relied upon for lookbacks and other important regulatory initiatives. At the same time, it will eliminate confusion within the industry and reduce the administrative burden associated with retrieving and analyzing archived hard-copy records that are difficult to maintain.

VII. Conclusion

ABRA appreciates the opportunity to comment on this important guidance. Although the nation's supply of blood and blood products is safe, we recognize the need to be vigilant about potential threats. Notwithstanding this, actions taken to address potential or theoretical threats must be carefully balanced against the impact of such actions on the regulated industry and, ultimately the consuming public. Moreover, the need to strictly adhere to administrative procedures and public process is most acute in the context of policy setting aimed at potential or theoretical threats.

Closer adherence to the public process with respect to the CJD Guidance must be obtained. The CJD Guidance should be reissued in draft to permit a more complete opportunity for public comment before it is implemented. In addition, the lookback requirements and the change in familial risk factors for classic CJD must undergo advisory committee and public scrutiny before they are implemented. Finally, the Agency should define what constitutes "readily retrievable records" before it mandates actions based on this otherwise nebulous standard.

If you have any questions about these comments or would like additional information, please contact Chris Healey, Senior Director of Government Affairs for ABRA, at 410.263.8396.

Respectively submitted,

Christopher P. Healey
Senior Director, Government Affairs

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